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The safety of levothyroxine use with respect to bone mineral density

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Abstract

Background: Previous studies on bone mineral density (BMD) abnormalities associated with hypothyroidism are scarce and not conclusive. The effect of thyroid hormone therapy on BMD has shown mixed results.

Aim: This study aimed primarily to determine the association between the positive history of levothyroxine administering and the risk of osteoporotic fracture in Jordanian cohort of both genders, including post-menopausal women, who were attended to our rehabilitation clinic.

Methods: This study trial was an observational study, which was conducted retrospectively at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid, Jordan. The Binary Logistic Regression (BLgR) analysis was conducted for the 2 contrarily Levothyroxine (Tx) comparative group; Tx dependent cohort (Cohort II) versus Non-Tx dependent cohort (Cohort I), against the probability of being on the higher (versus lower) risk of femoral hip osteoporotic fracture (fHOPF). The studied patients were dichotomously categorized into 2 comparative cohorts; non-Levothyroxine dependent cohort [Cohort I] versus Levothyroxine dependent cohort [Cohort II]. A Chi Square test was processed across these 2 dichotomized cohorts to express the comparison results as Number (Percentages), strength of associations (odd ratios), Pearson chi-square statistic (χ 2), Goodness of Fit (G-Test of independence), and Pearson (r) and Spearman (ρ) correlations.

Results: The BLgR analysis results revealed that the unadjusted risk ratio for the higher probability of fHOPF in our investigated patients, who were on Thyroxine therapy [Tx dependent cohort, Cohort II] compared to the Tx independent cohort [Cohort I], was 10.969 (95% CI; 4.615-26.072). The explained variations in the fHOPF risk related Tx dependent status on our model of this BLgR based model ranged from 17.9%-23.8% (depending on the inferential Cox & Snell R^2 or Nagelkerke R^2 methods, respectively) and correctly classified approximately 61.2% of the overall cases. The constructed BLgR model was formulated as {e (-0.627+2.395×Tx)/[1+ e (-0.627+2.395×Tx)]}.

Conclusion: We revealed that the patients who were used thyroxine therapies (Cohort II patients) had significantly higher proportional distribution of higher risk of fHOPF compared to Cohort I patients [41 (85.4%) vs 55 (34.8%), respectively] with an odd ratio of 10.969 (95% CI; 4.62-26.07) and significant positive correlation of 0.429±0.057, χ2=37.889, p-value=0.000.

Keywords: Levothyroxine; Bone mineral density; Osteoporotic fracture; Safety issues

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1. Introduction

According to the World Health Organization (WHO), osteoporosis is considered one of the most physical and quality disability aging, or pathologically in some cases, related disorder. It is numerically defined as T-Score ≤−2.5 SD from the referenced young population's bone mineral density (BMD) mean. Of Note, 0<T score<-1 is considered a normal state and -1≤ T-Score<-2.5 is considered as an osteopenia state. While -2.5≤ T-Score with a positive related risk factors for osteoporotic fracture, is considered as a severe osteoporosis state. In several cases, the T-Score is within the osteopenia range but the Fracture Risk Assessment Tool (FRAX) is ≥ 3% or ≥20% for the 10-year probabilities of hip osteoporotic fracture or vertebral major osteoporotic fracture, respectively. In these aforementioned case's scenarios, the assessed patients are also considered as a severe osteoporosis state [1-4].

While it is most likely be treatable, the thyroid disorder is one of the utmost endocrinology and non-endocrinology pathologies that have direct or indirect negative impacts on bone quality and quantity in both short- and long-term statuses. The complex correlations between thyroid functionality and overall architectural bone metabolism is firstly reported at 1891 by Von Recklinghausen, which explained a significant positive correlation that integrates both hyperthyroidism and osteoporotic fracture. Regarding this negative association of hyperthyroidism against osteoporotic fracture, several studies stated that chronic hyperthyroidism state has been shown to deteriorate both bone quality/quantity and consequently amplify the osteoporotic fracture risk, especially in post-menopausal women and other aged men. Indeed, other interventional studies, revealed that 1-year post-hyperthyroidism management can significantly mitigate the propensity of patients' osteoporotic fracture risks [5-9].

In the other side, hypothyroidism which is also a common endocrinology disorder and affecting approximately 1% of the overall population, has a bidirectional clinical impact on bone health. Firstly, studies showed that administering levothyroxine for primary hypothyroidism is critical for normal bone growth and subsequently bone quality and quantity. Oppositely, exceeding the recommended requirement of levothyroxine, has a negatively impact on bone architecture. Biochemically, overt hypothyroidism is defined as a concentration free total thyroxine (T4) lower the lower limit with accompanied higher than upper limit of thyroid-stimulating hormone (TSH). Additionally, the subclinical hypothyroidism has usually a normal T4 level accompanied mostly with elevated TSH level. So that, contradictory results were observed regarding the association between levothyroxine administering and osteoporotic fracture risk. Generally, studies' results revealed that using a higher dose of levothyroxine raised the probability of fracture compared to lower doses and a lower bone density and quality reported with larger versus lower levothyroxine replacement dosing. Other studies concluded that long-term levothyroxine administering does not significantly impact the bone mineral density and hence the development of osteoporotic fractures [10-14].

However, there are limited data discussed the complex multi-directional associations of endogenously T4 levels, TSH, levels, exogenously administering levothyroxine, and the net clinical impacts on bone architectural, especially in the Middle Eastern countries, including Jordanian cohort. Therefore, this study aimed primarily to determine the association between the positive history of levothyroxine administering and the risk of osteoporotic fracture in Jordanian cohort of both genders, including post-menopausal women, who were attended to our rehabilitation clinic.

2. Material and methods

This study trial was an observational study, which was conducted retrospectively at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid, Jordan. Exclusion criteria including but not excluded to, renal or non-renal metabolic osteodystrophy and bone metastatic. The Age-adjusted Charlson Co-Morbidity Index (AACCI) and Functionality Grade system were used for the co-morbidity burden and overall functionality assessment purposes, respectively. Dual-emission X-ray absorptiometry (DEXA) scans of the proximal femoral hip and anteroposterior spine participant's data were used to collect the Hip and Lumbar T and Z-Scores, respectively.

The Binary Logistic Regression (BLgR) analysis was conducted for the 2 contrarily Levothyroxine (Tx) comparative group; Tx dependent cohort (Cohort II) versus Non-Tx dependent cohort (Cohort I), against the probability of being on the higher (versus lower) risk of femoral hip osteoporotic fracture (fHOPF), to explore the degree of correlations, determine how much of total variations in the dependent variable can be explained by the independent variables, and assess the quality of the prediction of the dependent variable. In this study, the higher probability of fHOPF was determined as either T-Score is <-2.5 (regardless of FRAX is < or ≥ 3%) or T-Score is between -1 and -2.5 but the FRAX is ≥3%. In contrast, the lower probability of fHOPF was determined as T-Score is between -1 and -2.5, and the FRAX is <3% or the T-Score is >-1 (regardless of FRAX is ≥ or <3%). The higher probability of fHOPF is considered as a Positive state and the lower probability of fHOPF is considered as a Negative State. For the tested categorical Tx related

independent variable, 0 was assigned for the Cohort I and was considered the reference. While 1 was assigned for the Cohort II.

The studied patients were dichotomously categorized into 2 comparative cohorts; non-Levothyroxine dependent cohort [Cohort I] versus Levothyroxine dependent cohort [Cohort II]. A Chi Square test was processed across these 2 dichotomized cohorts to express the comparison results as Number (Percentages), strength of associations (odd ratios), Pearson chi-square statistic (χ 2), Goodness of Fit (G-Test of independence), and Pearson (r) and Spearman (ρ) correlations. Statistical analysis was performed using Statistical Package for Social Science (SPSS) software version 23.0. Statistical significance was set at 5%.

3. Results

The BLgR analysis results revealed that the unadjusted risk ratio for the higher probability of fHOPF in our investigated patients, who were on Thyroxine therapy [Tx dependent cohort, Cohort II] compared to the Tx independent cohort [Cohort I], was 10.969 (95% CI; 4.615-26.072). The explained variations in the fHOPF risk related Tx dependent status on our model of this BLgR based model ranged from 17.9%-23.8% (depending on the inferential Cox & Snell R^2 or Nagelkerke R^2 methods, respectively) and correctly classified approximately 61.2% of the overall cases. The constructed BLgR model was formulated as {e (-0.627+2.395×Tx) / [1+ e (-0.627+2.395×Tx)]}.

The overall tested gender's ratio (female to male ratio) in this study was assigned to 5.87: 1 with insignificant distributions across the non-Tx dependent cohort (Cohort I) and the Tx dependent cohort (Cohort II) [6.18: 1 and 5: 1, respectively, 1.236 (95% CI; 0.511-2.989), 0.033±0.072, χ 2=0.223, p-value=0.637]. The tested patients' age ranges were significantly distributed between Cohort I-II, in which the patients' age ranges negatively and significantly correlated with the Tx dependency [-0.234±0.072, χ 2=13.172, p-value=0.010].

According to the 2 investigated osteoporosis assessment tools; the Osteoporosis Assessment Tool (OST, -20-+20) and the Osteoporosis Risk Assessment Instrument (ORAI, 0-26), our study revealed positive correlations for the OST and ORAI against Tx dependency cohorts [0.122±0.073 and 0.190±0.058, respectively] which it was insignificant in case of OST and significant in case of ORAI [χ 2=3.058 and 11.311, p-value=0.217 and 0.003, respectively]. All the tested patients' analysis results and illustrations were clearly and fully presented in Table 1-3 and Figure 1-2.

Table 1 The Binary Logistic Regression analysis for the Cohort II versus Cohort I in the Jordanian investigated patients, who attended to the rehabilitation clinic between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid/Jordan, against the probability of having fHOPF

Tested predictors	**B±SEM**	**Wald**	**Sig.**	**Exp (B)**	**95% C.I. for EXP(B)**		**VR**	**%Cases**
					Lower	Upper		
Higher fHOPF (Prob%)	e (-0.627+2.395×Tx)/[1+ e (-0.627+2.395×Tx)]							
Tx vs non-Tx	2.395±0.442	29.396	0.000	10.969	4.615	26.072	17.9%-23.8%	61.2%
Constant	-0.627±0.167	14.113	0.000	0.534				

The Binary Logistic Regression (BLgR) analysis was conducted for the 2 contrarily Levothyroxine (Tx) comparative group; Tx dependent cohort (Cohort II) versus Non-Tx dependent cohort (Cohort I), against the probability of being on the higher (versus lower) risk of femoral hip osteoporotic fracture (fHOPF), to explore the degree of correlations, determine how much of total variations in the dependent variable can be explained by the independent variables, and assess the quality of the prediction of the dependent variable.

In this study, the higher probability of fHOPF was determined as either T-Score is <-2.5 (regardless of FRAX is < or ≥ 3%) or T-Score is between -1 and -2.5 but the FRAX is ≥3%. In contrast, the lower probability of fHOPF was determined as T-Score is between -1 and -2.5, and the FRAX is <3% or the T-Score is >-1 (regardless of FRAX is ≥ or <3%). The higher probability of fHOPF is considered as a Positive state and the lower probability of fHOPF is considered as a Negative State. For the tested categorical Tx related independent variable, 0 was assigned for the Cohort I and was considered the reference. While 1 was assigned for the Cohort II.

Table 2 The comparatively studied variables across the Cohort I-II; Non-Tx dependent cohort (Cohort I) versus Tx dependent cohort (Cohort II), for the Jordanian investigated patients, who attended to the rehabilitation clinic between Sep 2021 and Nov 2021 at the Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid/Jordan

	Non-Tx Cohort [Cohort I] (158, 76.69%)	**Tx Cohort [Cohort II] (48, 23.30%)**	**Total (206, 100%)**	**OR**	**R ρ**	**χ^2 G-Test**	**p-Value**
Gender							
Female	136 (86.1%)	40 (83.3%)	176 (85.4%)	1.236 (95% CI; 0.511-2.989)	0.033±0.072 0.033±0.072	0.223 0.217	0.637 0.641
Male	22 (13.9%)	8 (16.7%)	30 (14.6%)				
Female: Male	6.18: 1	5: 1	5.87: 1				
Age (Yrs)							
0-39	7 (4.4%)	8 (16.7%)	15 (7.3%)	NA	-0.234±0.072* -0.221±0.069*	13.172 12.254	0.010 0.016
40-49	13 (8.2%)	6 (12.5%)	19 (9.2%)				
50-59	47 (29.7%)	18 (37.5%)	65 (31.6%)				
60-69	57 (36.1%)	10 (20.8%)	67 (32.5%)				
>=70	34 (21.5%)	6 (12.5%)	40 (19.4%)				
Post-Menopausal age							
40-44.9	10 (7.6%)	5 (12.5%)	15 (8.7%)	NA	-0.040±0.076 -0.027±0.077	1.782 1.749	0.619 0.626
45-49.9	61 (46.2%)	16 (40.0%)	77 (44.8%)				
50-54.9	46 (34.8%)	16 (40.0%)	62 (36.0%)				
>=55	15 (11.4%)	3 (7.5%)	18 (10.5%)				
OST (-20-20)							
Low risk (-1-20)	103 (65.2%)	25 (52.1%)	128 (62.1%)	NA	0.122±0.073 0.120±.072	3.058 2.950	0.217 0.229
Moderate risk (-4--1)	46 (29.1%)	18 (37.5%)	64 (31.1%)				
High risk (-20- -4)	9 (5.7%)	5 (10.4%)	14 (6.8%)				

Data results of the comparative variables between the 2 tested cohorts were statistically analyzed by Chi-Square Test (at p-value< 0.05) and expressed as Numbers (Percentage). The strength of associations was also described as odd ratios (OR). The Pearson chi-square statistic (χ 2) involves the squared difference between the observed and the expected frequencies. The Goodness of Fit (G-Test of independence) uses the log of the ratio of two likelihoods and tests the goodness of fit of observed frequencies to their expected. Both the interval by interval (Pearson, r) and the ordinal by ordinal (Spearman, ρ) correlations were expressed as value± standard error of value. The studied patients were dichotomously categorized into 2 comparative cohorts; Non-Levothyroxine dependent cohort (Cohort I) versus Levothyroxine dependent cohort (Cohort II).

OST: The Osteoporosis self-Assessment Tool.

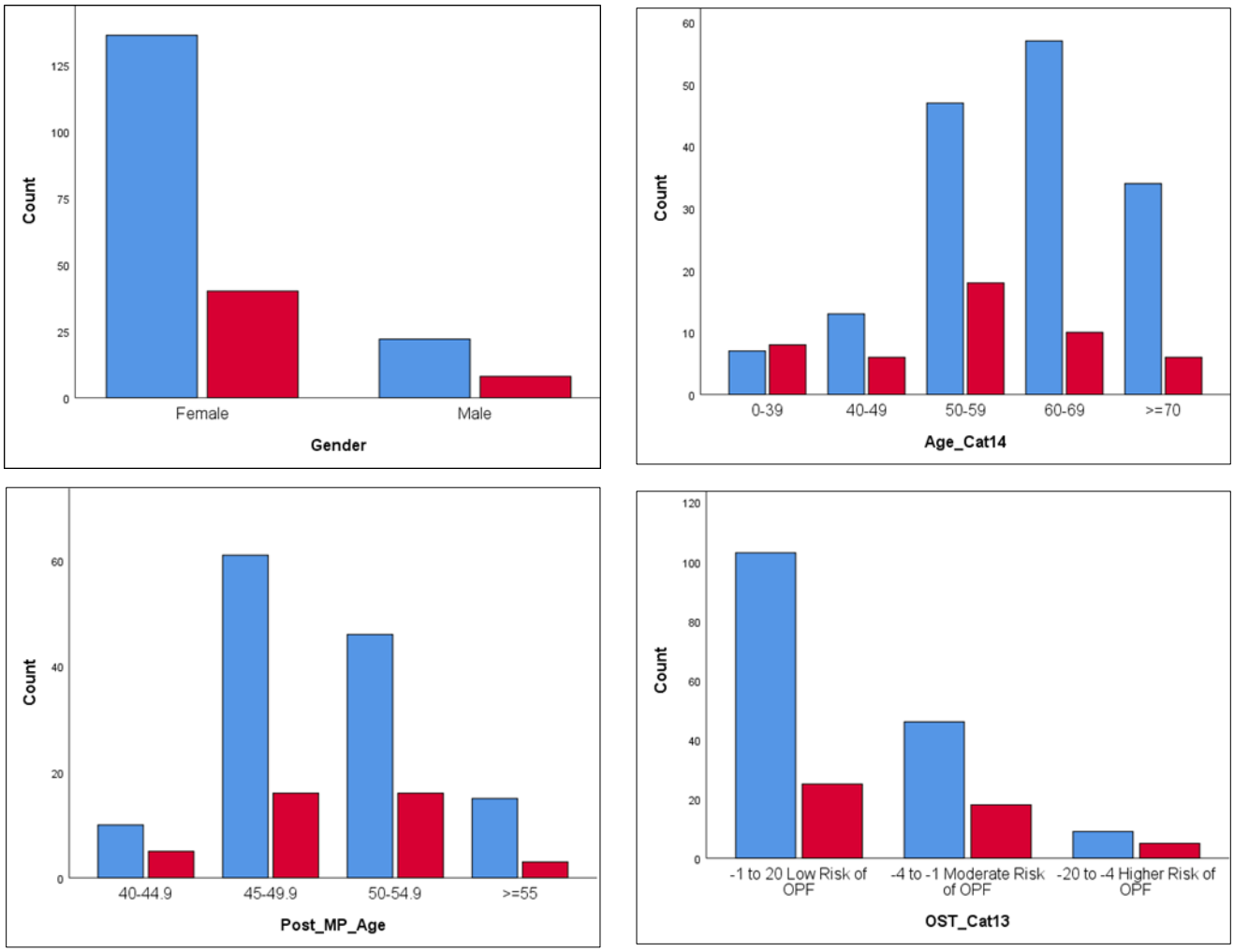

Figure 1 The bar charts' visualizations for the studied patients across the Cohort I-II; Non-Tx dependent cohort (Cohort I) versus Tx dependent cohort (Cohort II), for the Jordanian investigated patients, who attended to the rehabilitation clinic between Sep 2021 and Nov 2021 at the Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid/Jordan

Table 3 The comparatively studied variables across the Cohort I-II; Non-Tx dependent cohort (Cohort I) versus Tx dependent cohort (Cohort II), for the Jordanian investigated patients, who attended to the rehabilitation clinic between Sep 2021 and Nov 2021 at the Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid/Jordan.

	Non-Tx Cohort [Cohort I] (158, 76.69%)	**Tx Cohort [Cohort II] (48, 23.30%)**	**Total (206, 100%)**	**OR**	**R ρ**	**χ 2 G-Test**	**p-Value**
ORAI (0-26)							
Low risk (0-8)	42 (28.4%)	1 (2.6%)	43 (23.1%)	NA	0.190±0.058* 0.188±0.059*	11.311 15.360	0.003 0.000
Moderate risk (9-15)	70 (47.3%)	25 (65.8%)	95 (51.1%)				
High risk (16-25)	36 (24.3%)	12 (31.6%)	48 (25.8%)				
fH_BMD (g/cm2)							

<0.755	62 (39.2%)	41 (85.4%)	103 (50.0%)	0.110 (95% CI; 0.047-0.261)	-0.390±0.057* -0.390±0.057*	31.400 34.036	0.000 0.000
≥0.755	96 (60.8%)	7 (14.6%)	103 (50.0%)				
ACCI							
<4	126 (79.7%)	6 (12.5%)	132 (64.1%)	27.563 (95% CI; 10.77-70.51)	0.593±0.056* 0.593±0.056*	72.328 73.624	0.000 0.000
≥4	32 (20.3%)	42 (87.5%)	74 (35.9%)				
fHOPF risk							
Lower	103 (65.2%)	7 (14.6%)	110 (53.4%)	10.969 (95% CI; 4.62-26.07)	0.429±0.057* 0.429±0.057*	37.889 40.526	0.000 0.000
Higher	55 (34.8%)	41 (85.4%)	96 (46.6%)				
Functionality							
Lower	67 (42.4%)	24 (50.0%)	91 (44.2%)	0.736 (95% CI; 0.385-1.407)	-0.065±0.070 -0.065±0.070	0.861 0.857	0.353 0.355
Higher	91 (57.6%)	24 (50.0%)	115 (55.8%)				
Vit D (ng/ml)							
<30	102 (64.6%)	41 (85.4%)	143 (69.4%)	0.311 (95% CI; 0.131-0.739)	-0.191±0.058* -0.191±0.058*	7.546 8.351	0.006 0.004
≥30	56 (35.4%)	7 (14.6%)	63 (30.6%)				

Data results of the comparative variables between the 2 tested cohorts were statistically analyzed by Chi-Square Test (at p-value< 0.05) and expressed as Numbers (Percentage). The strength of associations was also described as odd ratios (OR). The Pearson chi-square statistic (χ 2) involves the squared difference between the observed and the expected frequencies. The Goodness of Fit (G-Test of independence) uses the log of the ratio of two likelihoods and tests the goodness of fit of observed frequencies to their expected. Both the interval by interval (Pearson, r) and the ordinal by ordinal (Spearman, ρ) correlations were expressed as value± standard error of value. The studied patients were dichotomously categorized into 2 comparative cohorts; Non-Levothyroxine dependent cohort (Cohort I) versus Levothyroxine dependent cohort (Cohort II).

In this study, the higher probability of fHOPF was determined as either T-Score is <-2.5 (regardless of FRAX is < or ≥ 3%) or T-Score is between -1 and -2.5 but the FRAX is ≥3%. In contrast, the lower probability of fHOPF was determined as T-Score is between -1 and -2.5, and the FRAX is <3% or the T-Score is >-1 (regardless of FRAX is ≥ or <3%). The higher probability of fHOPF is considered as a Positive state and the lower probability of fHOPF is considered as a Negative State. For the tested categorical Tx related independent variable, 0 was assigned for the Cohort I and was considered the reference. While 1 was assigned for the Cohort II.

ACCI: Age-adjusted Charlson Comorbidity Index. ORAI: The Osteoporosis Risk Assessment Instrument.	fHOPF: Femoral hip osteoporotic fracture.

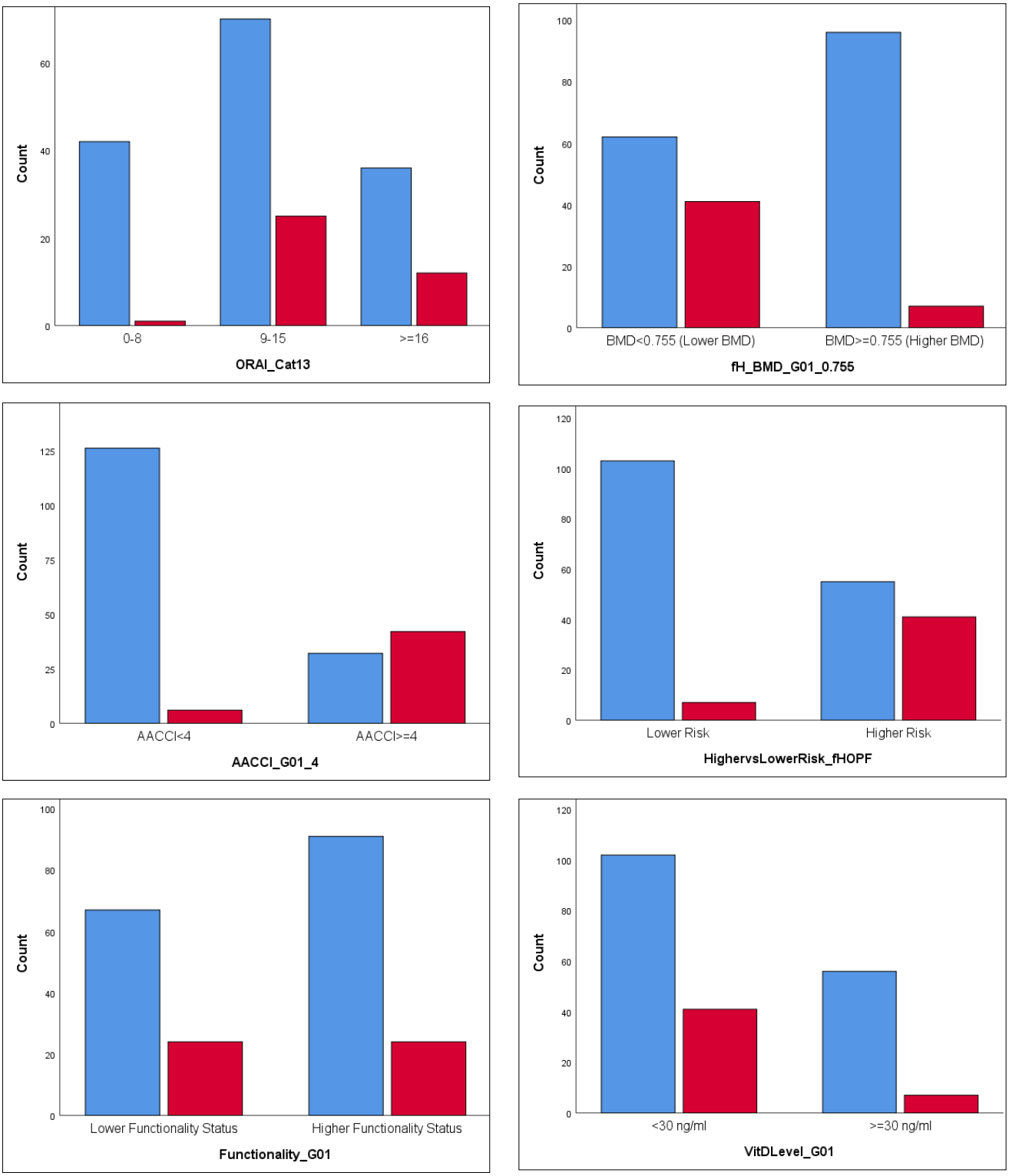

Figure 2 The bar charts' visualizations for the studied patients across the Cohort I-II; Non-Tx dependent cohort (Cohort I) versus Tx dependent cohort (Cohort II), for the Jordanian investigated patients, who attended to the rehabilitation clinic between Sep 2021 and Nov 2021 at Prince Rashid bin Al-Hasan Military Hospital, Royal Medical Services, Irbid/Jordan

4. Discussion

Clinically, the effect of thyroid hormone therapy on BMD has shown mixed results. Several previous studies had shown that patients with untreatable or uncontrolled hyperthyroidism, their bone quality and quantity were significantly dampened toward a negative balance in bone formation. Moreover, there is growing evidences for direct association between low TSH and Low BMD. Approximately the risk of vertebral and non-vertebral osteoporotic fractures increases 3-4 folds with serum TSH levels ≤0.1 IU/L [15-17].

While initial treatment of hypothyroidism condition with thyroid hormones to achieve an euthyroid status improves the architectural structure of bone and overall growth, especially in younger populations, excess thyroxine administering, as indicated by lowering the serum TSH <0.1 IU/L like hyperthyroidism, will similarly thinning the cortical bone layers and consequently facilitate the propensity for osteoporotic fracture risk. Additionally, supra-levothyroxine supplementation might increase arrythmia risk and the liability for falling related fractures [18-22].

In our study, we revealed that the patients who were used thyroxine therapies (Cohort II patients) had significantly higher proportional distribution of higher risk of fHOPF compared to Cohort I patients [41 (85.4%) vs 55 (34.8%), respectively] with an odd ratio of 10.969 (95% CI; 4.62-26.07) and significant positive correlation of 0.429±0.057, χ^2=37.889, p-value=0.000. Although the investigated patients who belonged to the Tx dependent cohort (Cohort II) had significantly lower proportional percentage for fH_BMD ≥0.755 g/cm^2 than in the compared tested patients who belonged to the Tx independent cohort (Cohort I) [7 (14.6%) vs 96 (60.8%), respectively, 0.110 (95% CI; 0.047-0.261), -0.390±0.057, χ2=31.400, p-value=0.000].

5. Conclusion

We revealed that the patients who were used thyroxine therapies (Cohort II patients) had significantly higher proportional distribution of higher risk of fHOPF compared to Cohort I patients [41 (85.4%) vs 55 (34.8%), respectively] with an odd ratio of 10.969 (95% CI; 4.62-26.07) and significant positive correlation of 0.429±0.057, χ2=37.889, p-value=0.000.

Compliance with ethical standards

Acknowledgement

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Disclosure of conflict of interest

There is no conflict of interest in this manuscript

Statement of ethical approval

There is no animal/human subject involvement in this manuscript

Statement of informed consent

Owing to the retrospective design of this study, the informed consent form was waived.

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